



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/415, C07D 233/66, 233/90,</b> <b>233/60, 233/54, 233/61</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/27852</b> <b>(43) International Publication Date:</b> 7 August 1997 (07.08.97)
<b>(21) International Application Number:</b> PCT/US97/01354 <b>(22) International Filing Date:</b> 27 January 1997 (27.01.97)  <b>(30) Priority Data:</b> 60/010,798                      30 January 1996 (30.01.96)                      US 9605708.8                      19 March 1996 (19.03.96)                      GB  <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DINSMORE, Christopher, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HARTMAN, George, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE  <b>(57) Abstract</b> <p>The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.</p>		

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## TITLE OF THE INVENTION

### INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

## BACKGROUND OF THE INVENTION

5           The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

20           Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa<sup>1</sup>-Aaa<sup>2</sup>-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C<sub>15</sub> or C<sub>20</sub> isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational

- 2 -

farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side

- 3 -

effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, *et al.*, *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and thereapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to

- 4 -

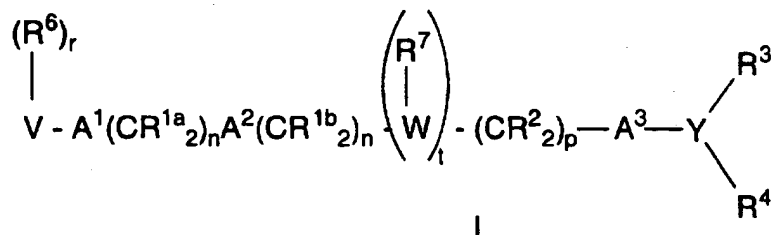
develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

## 5 SUMMARY OF THE INVENTION

The present invention comprises small molecule peptidomimetic amide-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior  
 10 in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

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The compounds of this invention are illustrated by the formula I:

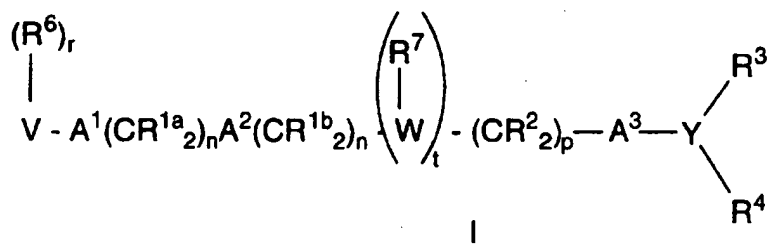


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## DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of  
 25 farnesyl-protein transferase are illustrated by the formula I:

- 5 -



wherein:

R<sup>1a</sup>, R<sup>1b</sup> and R<sup>2</sup> are independently selected from:

- 5        a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-,
- 10       c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)-NR<sup>8</sup>-;

- 15       R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, CF<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>O-, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl,
- 20       substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R<sup>5</sup> is selected from:

- 25       a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocyclic,
- d) unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, and
- e) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl,

- 6 -

unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

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R<sup>6</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, R<sup>8</sup><sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NH-, CN, H<sub>2</sub>N-C(NH)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>8</sup>OC(O)NH-;

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R<sup>7</sup> is selected from:

- a) hydrogen,
- b) C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>N-C-(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-;

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R<sup>8</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and aryl;

R<sup>9</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-,



- 7 -

-C(O)-, -C(O)NR<sup>8</sup>-, -NR<sup>8</sup>C(O)-, O, -N(R<sup>8</sup>)-,  
-S(O)<sub>2</sub>N(R<sup>8</sup>)-, -N(R<sup>8</sup>)S(O)<sub>2</sub>-, or S(O)<sub>m</sub>;

A<sup>3</sup> is selected from: -NR<sup>5</sup>C(O)- or -C(O)NH-;

5

V is selected from:

- a) hydrogen,
  - b) heterocycle,
  - c) aryl,
  - 10 d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are  
replaced with a heteroatom selected from O, S, and N,  
and
  - e) C<sub>2</sub>-C<sub>20</sub> alkenyl,
- provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen  
15 if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

W is a heterocycle;

Y is aryl or heteroaryl;

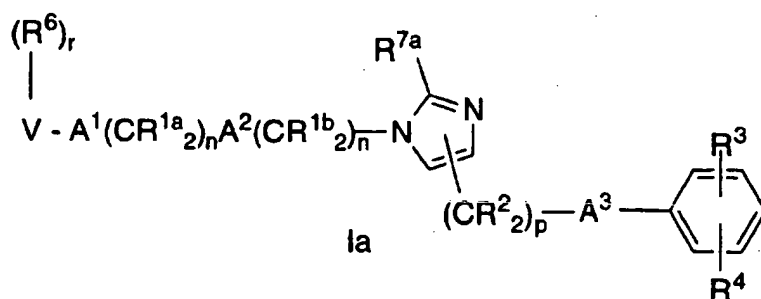
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- m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- r is 0 to 5, provided that r is 0 when V is hydrogen; and
- 25 t is 0 or 1;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this  
30 invention are illustrated by the formula Ia:

- 8 -



wherein:

- 5 R<sup>1a</sup> and R<sup>1b</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

- 10 a) hydrogen,  
 b) aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub> alkenyl,  
 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;

- 15 R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;
- 20

R<sup>5</sup> is selected from:

- a) hydrogen,  
 and  
 25 b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-,

- 9 -

$(R^9)S(O)_m-$ ,  $(R^8)C(O)NH-$ ,  $H_2N-C(NH)-$ ,  $(R^8)C(O)-$ ,  
 $(R^8)OC(O)-$ ,  $N_3$ ,  $CN$   $(R^9)OC(O)NR^8-$ ;

$R^6$  is independently selected from:

- 5       a) hydrogen,
- b)  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_1-C_6$  perfluoroalkyl, F, Cl,  $R^8O-$ ,  $R^8C(O)NR^8-$ , CN,  $NO_2$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$ , or  $R^9OC(O)NR^8-$ , and
- 10       c)  $C_1-C_6$  alkyl substituted by  $C_1-C_6$  perfluoroalkyl,  $R^8O-$ ,  $R^8C(O)NR^8-$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$ , or  $R^9OC(O)NR^8-$ ;

$R^{7a}$  is hydrogen or methyl;

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$R^8$  is independently selected from hydrogen,  $C_1-C_6$  alkyl, benzyl and aryl;

$R^9$  is independently selected from  $C_1-C_6$  alkyl and aryl;

20

$A^1$  and  $A^2$  are independently selected from: a bond,  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-C(O)-$ ,  $-C(O)NR^8-$ , O,  $-N(R^8)-$ , or  $S(O)_m$ ;

$A^3$  is selected from:  $-NR^5C(O)-$  or  $-C(O)NH-$ ;

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V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
- 30       c) aryl,
- d)  $C_1-C_{20}$  alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

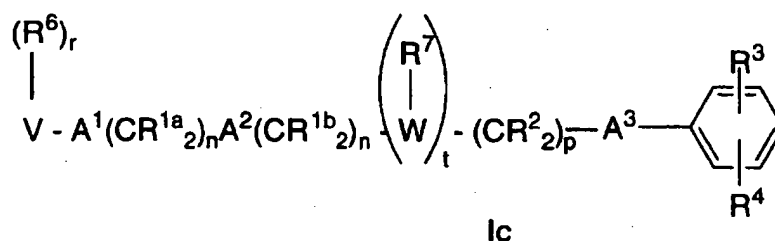
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e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and  
provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen  
if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

- 5    m is            0, 1 or 2;  
     n is            0, 1, 2, 3 or 4;  
     p is            0, 1, 2, 3 or 4; and  
     r is            0 to 5, provided that r is 0 when V is hydrogen;

10   or the pharmaceutically acceptable salts thereof.

A second preferred embodiment of the compounds of this  
invention are illustrated by the formula Ic:



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wherein:

R<sup>1a</sup> and R<sup>1b</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub>  
alkyl;

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R<sup>2</sup> is independently selected from:

- a) hydrogen,  
b) aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub>  
alkenyl,  
25    c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,  
heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;

R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>,  
NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-

- 11 -

C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN,  
(R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or  
unsubstituted aryl and substituted or unsubstituted  
heterocycle;

5

R<sup>5</sup> is selected from:

a) hydrogen,  
and

10 b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group  
selected from unsubstituted or substituted aryl,  
unsubstituted or substituted heterocyclic, unsubstituted or  
substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-,  
(R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-,  
(R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

15

R<sup>6</sup> is independently selected from:

a) hydrogen,

20 b) C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub>  
perfluoroalkyl, F, Cl, R<sup>8</sup>O-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>,  
(R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, -N(R<sup>8</sup>)<sub>2</sub>, or  
R<sup>9</sup>OC(O)NR<sup>8</sup>-, and  
c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>8</sup>O-,  
R<sup>8</sup>C(O)NR<sup>8</sup>-, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-,  
-N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-;

25

R<sup>7</sup> is selected from: hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>8</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and  
aryl;

30

R<sup>9</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-,  
-C(O)-, -C(O)NR<sup>8</sup>-, O, -N(R<sup>8</sup>)-, or S(O)<sub>m</sub>;

- 12 -

A<sup>3</sup> is selected from: -NR<sup>5</sup>C(O)- or -C(O)NH-;

V is selected from:

- 5           a) hydrogen,  
          b) heterocycle selected from pyrrolidinyl, imidazolyl,  
              pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl,  
              quinolinyl, isoquinolinyl, and thienyl,  
          c) aryl,  
10          d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are  
              replaced with a heteroatom selected from O, S, and N,  
              and

          e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

- provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen  
15 if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

W is a heterocycle selected from pyrrolidinyl, pyridinyl, thiazolyl,  
pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

- 20 m is           0, 1 or 2;  
n is            0, 1, 2, 3 or 4;  
p is            0, 1, 2, 3 or 4;  
r is            0 to 5, provided that r is 0 when V is hydrogen; and  
t is            1;

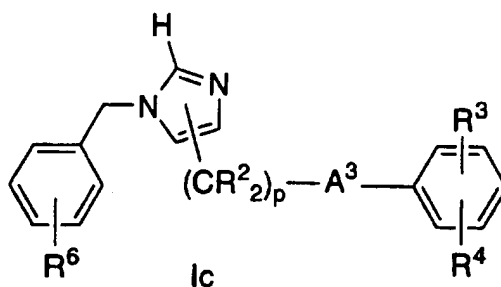
25

or the pharmaceutically acceptable salts thereof.

In a more preferred embodiment of this invention, the  
inhibitors of farnesyl-protein transferase are illustrated by the formula

30 Ic:

- 13 -



wherein:

R<sup>1b</sup> is independently selected from:

- 5       a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;

10

R<sup>2</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

15

20   R<sup>5</sup> is selected from:

- a) hydrogen,
- and

b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

25

- 14 -

$R^6$  is independently selected from:

- a) hydrogen,
- b)  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_1$ - $C_6$  perfluoroalkyl, F, Cl,  $R^8O$ -,  $R^8C(O)NR^8$ -, CN,  $NO_2$ ,  $(R^8)_2N-C(NR^8)$ -,  $R^8C(O)$ -,  $R^8OC(O)$ -,  $-N(R^8)_2$ , or  $R^9OC(O)NR^8$ -, and
- c)  $C_1$ - $C_6$  alkyl substituted by  $C_1$ - $C_6$  perfluoroalkyl,  $R^8O$ -,  $R^8C(O)NR^8$ -,  $(R^8)_2N-C(NR^8)$ -,  $R^8C(O)$ -,  $R^8OC(O)$ -,  $-N(R^8)_2$ , or  $R^9OC(O)NR^8$ -;

$R^8$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl, benzyl and aryl;

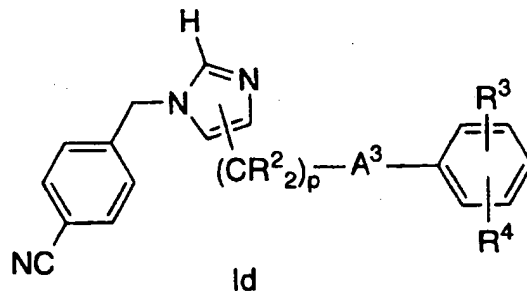
$R^9$  is independently selected from  $C_1$ - $C_6$  alkyl and aryl;

$A^3$  is selected from:  $-NR^5C(O)-$  or  $-C(O)NH-$ ;

$m$  is 0, 1 or 2; and  
 $p$  is 0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In a second more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula Id:





- 15 -

wherein:

$R^{1b}$  is independently selected from:

- a) hydrogen,
- 5      b) aryl, heterocycle, cycloalkyl,  $R^8O-$ ,  $-N(R^8)_2$  or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl,  $R^8O-$ , or  $-N(R^8)_2$ ;

10     $R^2$  are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

$R^3$  and  $R^4$  are independently selected from F, Cl, Br,  $N(R^8)_2$ , CF<sub>3</sub>, NO<sub>2</sub>,  $(R^8)O-$ ,  $(R^9)S(O)_m-$ ,  $(R^8)C(O)NH-$ , H<sub>2</sub>N-C(NH)-,  $(R^8)C(O)-$ ,  $(R^8)OC(O)-$ , N<sub>3</sub>, CN,  $(R^9)OC(O)NR^8-$ , C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

15

$R^5$  is selected from:

- 20      a) hydrogen,
- and
- b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  $N(R^8)_2$ , CF<sub>3</sub>, NO<sub>2</sub>,  $(R^8)O-$ ,  $(R^9)S(O)_m-$ ,  $(R^8)C(O)NH-$ , H<sub>2</sub>N-C(NH)-,  $(R^8)C(O)-$ ,  $(R^8)OC(O)-$ , N<sub>3</sub>, CN  $(R^9)OC(O)NR^8-$ ;
- 25

30     $R^8$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and aryl;

$R^9$  is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

$A^3$  is selected from:  $-NR^5C(O)-$  or  $-C(O)NH-$ ;

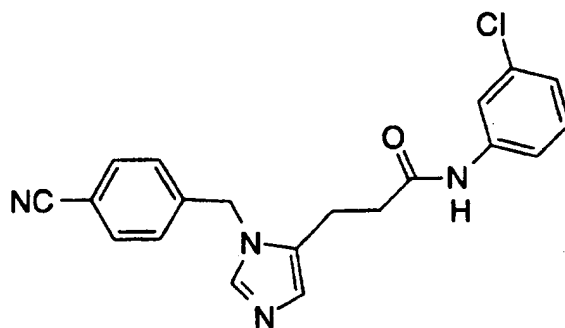
- 16 -

m is 0, 1 or 2; and  
p is 0, 1, 2, 3 or 4;

5 or the pharmaceutically acceptable salts thereof.

Specific examples of the compounds of the invention are:

*N*-(3-chlorophenyl)-3-[1-(4-cyanobenzyl)-5-imidazolyl]propionamide  
10 hydrochloride (1)



or the pharmaceutically acceptable salts thereof.

15 The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R<sup>1a</sup>, R<sup>2</sup> etc.) occurs more than one time in any  
20 constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the  
25 specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen

- 17 -

bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholiny, naphthyridiny, oxadiazolyl, 2-oxoazepiny, 2-oxopiperaziny, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperaziny, pyridyl, pyraziny, pyrazolidiny, pyrazolyl, pyridaziny, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydroquinoliny, thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazoliny, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group

- 18 -

consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, 5 dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, 10 tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substituents selected from 15 the group which includes but is not limited to F, Cl, Br, CF<sub>3</sub>, NH<sub>2</sub>, N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, NO<sub>2</sub>, CN, (C<sub>1</sub>-C<sub>6</sub> alkyl)O-, -OH, (C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>m</sub>-, (C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH-, H<sub>2</sub>N-C(NH)-, (C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)-, (C<sub>1</sub>-C<sub>6</sub> alkyl)OC(O)-, N<sub>3</sub>, (C<sub>1</sub>-C<sub>6</sub> alkyl)OC(O)NH- and C<sub>1</sub>-C<sub>20</sub> alkyl.

20 Lines drawn into the ring systems from substituents (such as from R<sup>3</sup>, R<sup>4</sup> etc.) indicate that the bond may be attached to any of the substitutable ring carbon atoms.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds 25 of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, 30 lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

- 19 -

It is intended that the definition of any substituent or variable (e.g., R<sup>1a</sup>, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R<sup>8</sup>)<sub>2</sub> represents -NHH, -NHCH<sub>3</sub>, -NHC<sub>2</sub>H<sub>5</sub>, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

10 Preferably, R<sup>1a</sup>, R<sup>1b</sup> and R<sup>2</sup> are independently selected from: hydrogen, -N(R<sup>8</sup>)<sub>2</sub>, R<sup>8</sup>C(O)NR<sup>8</sup>- or C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by -N(R<sup>8</sup>)<sub>2</sub>, R<sup>8</sup>O- or R<sup>8</sup>C(O)NR<sup>8</sup>-.

15 Preferably, R<sup>3</sup> and R<sup>4</sup> are independently selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, CN, NO<sub>2</sub>, R<sup>8</sup><sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>- and C<sub>1</sub>-C<sub>6</sub> alkyl.

Preferably, R<sup>5</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen, R<sup>9</sup>S(O)<sub>m</sub>-, CF<sub>3</sub>- or an unsubstituted or substituted aryl group.

20 Preferably, R<sup>6</sup> is selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, CN, NO<sub>2</sub>, R<sup>8</sup><sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>- and C<sub>1</sub>-C<sub>6</sub> alkyl.

Preferably, R<sup>7</sup> is hydrogen or methyl. Most preferably, R<sup>7</sup> is hydrogen.

25 Preferably, R<sup>8</sup> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl and benzyl.

Preferably, A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -C(O)NR<sup>8</sup>-, -NR<sup>8</sup>C(O)-, O, -N(R<sup>8</sup>)-, -S(O)<sub>2</sub>N(R<sup>8</sup>)- and -N(R<sup>8</sup>)S(O)<sub>2</sub>-.

30 Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, Y is selected from phenyl, pyridyl, furanyl and thienyl. More preferably, Y is phenyl.

Preferably, n and r are independently 0, 1, or 2.

Preferably p is 1, 2 or 3.

- 20 -

Preferably t is 1.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods.

- 5 Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

- 10 Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in Schemes 1-12, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R' and R'CH<sub>2</sub>-, as shown in the Schemes, represent the substituents R<sup>8</sup>, R<sup>9</sup> and  
15 others, depending on the compound of the instant invention that is being synthesized.

- These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation  
20 reactions described in the Schemes.

#### Synopsis of Schemes 1-12:

- The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the  
25 most part. Scheme 1 illustrates the synthesis of one of the preferred embodiments of the instant invention, wherein the variable W is present as a imidazolyl moiety that is substituted with a suitably substituted benzyl group. Substituted protected imidazole alkanols II can be prepared by methods known in the art. such as those described by F.  
30 Schneider, *Z. Physiol. Chem.*, 3:206-210 (1961) and C.P. Stewart, *Biochem. Journal*, 17:130-133(1923). Intermediate II can then be oxidized to the imidazole alkanoic acid by methods known in the art. Some imidazole alkanoic acids containing alkyl substituents on the carbon atoms of the imidazole ring can be prepared by hydrolysis of the

- 21 -

corresponding nitriles, which can be prepared by methods known in the art (see for example: *J. Med. Chem.*, 19:923 (1976)).

5       Benzylation and deprotection of the imidazole alkanoate ester provides intermediate IV which can be hydrolyzed to the acid V and coupled to a suitably substituted aniline VI to provide the instant compound VII.

      Schemes 2-5 illustrate syntheses of other suitably substituted alkanoate esters useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety.  
10       Similar synthetic strategies for preparing ester intermediates that incorporate other heterocyclic moieties for variable W are also well known in the art.

      The suitably substituted aniline V can be reacted with a variety of other carboxylic acids, such as VIII, as illustrated in Scheme  
15       6. The product IX can be deprotected to give the instant compound X. The product X is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine X can further be selectively protected to obtain XI, which can subsequently be reductively alkylated with a suitable  
20       aldehyde, such as XII, to obtain XIII. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XIV can be accomplished by literature procedures.

      If the aniline V is coupled to an acid which also has a protected hydroxyl group, such as XV in Scheme 7, the protecting  
25       groups can be subsequently removed to unmask the hydroxyl group (Schemes 7 and 8). The primary alcohol XVI can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XVIII. In addition, the fully  
30       deprotected amino alcohol XIX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXX (Scheme 8), or tertiary amines.

      The Boc protected amino alcohol XVIa can also be utilized to synthesize aziridines such as XXI (Scheme 9). Treating XVIa with

- 22 -

1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide leads to the formation of aziridine XXI. The aziridine can be reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXII, which  
5 can be deprotected to provide the instant compound.

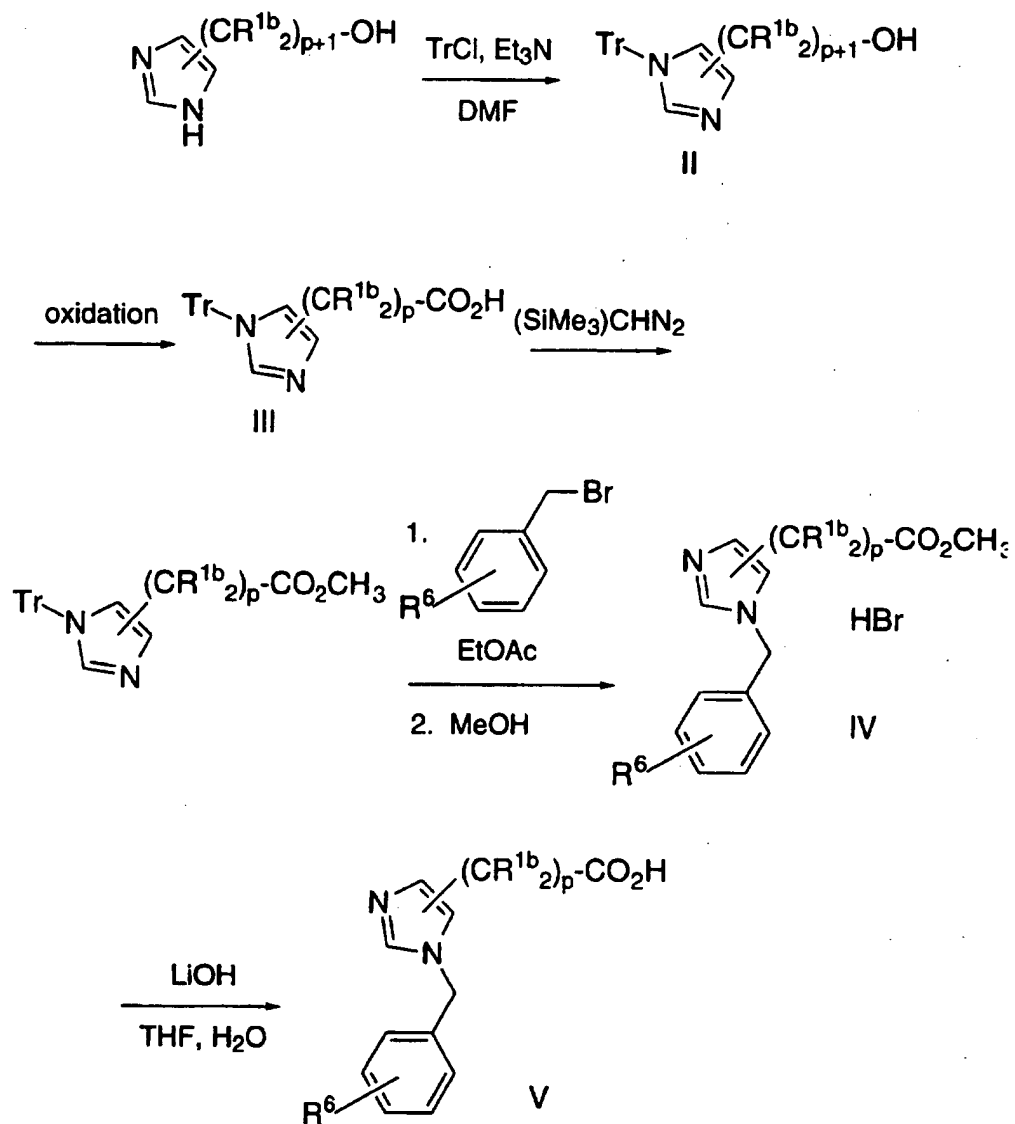
In addition, the aniline V can be reacted with acids derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXVI. When R' is an aryl  
10 group, XXVI can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXVII. Alternatively, the amine protecting group in XXVI can be removed, and O-alkylated phenolic amines such as XXVIII produced.

Schemes 11-12 illustrate the preparation of compounds of the instant invention wherein the orientation of the A<sup>3</sup> amide moiety is reversed relative to the compounds of Schemes 1-10. Thus the alkanol  
15 II may be protected and converted to the corresponding amine XXX via the azide, as shown in Scheme 11. Alternatively, if the appropriately substituted protected amine, such as a protected histamine XXXI, is available, that reagent may be ring alkylated to provide the intermediate  
20 amine XXXII.

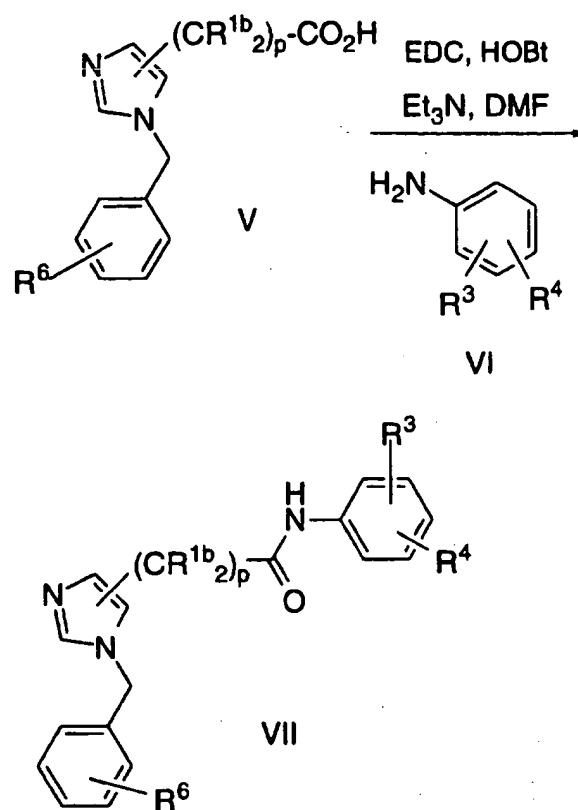
As shown in Scheme 12, an amine such as intermediate XXX may be reacted with a suitably substituted benzoic acid, such as compound XXXIII, to provide the instant compound XXXIV. The carbamate nitrogen of XXXIV may be subsequently alkylated as  
25 described previously in Scheme 1.



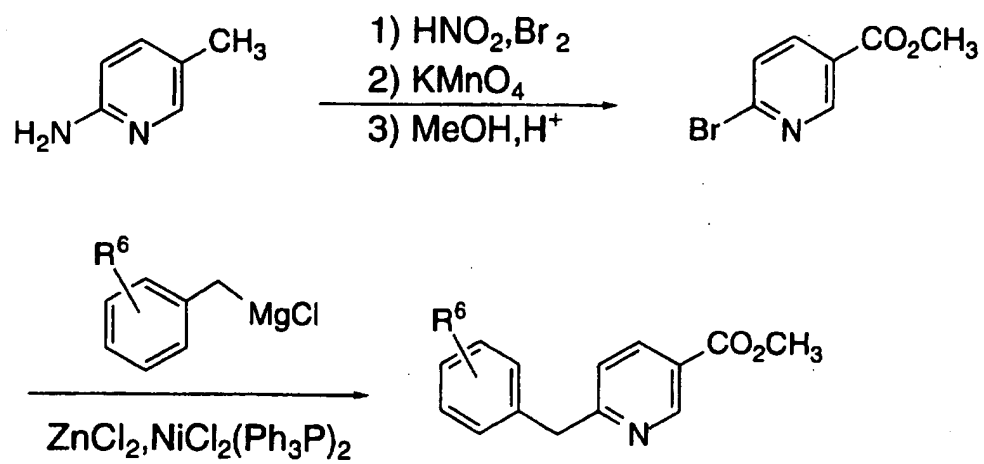
- 23 -

SCHEME 1

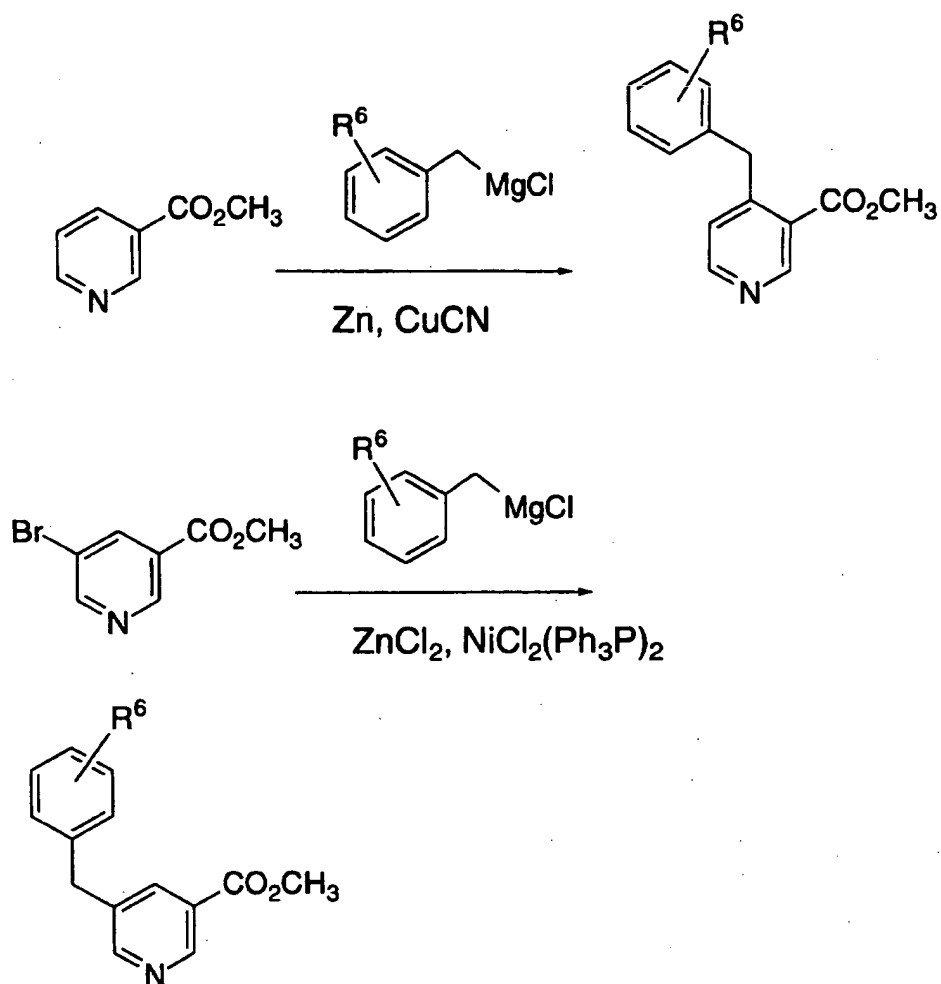
- 24 -

SCHEME 1 (continued)

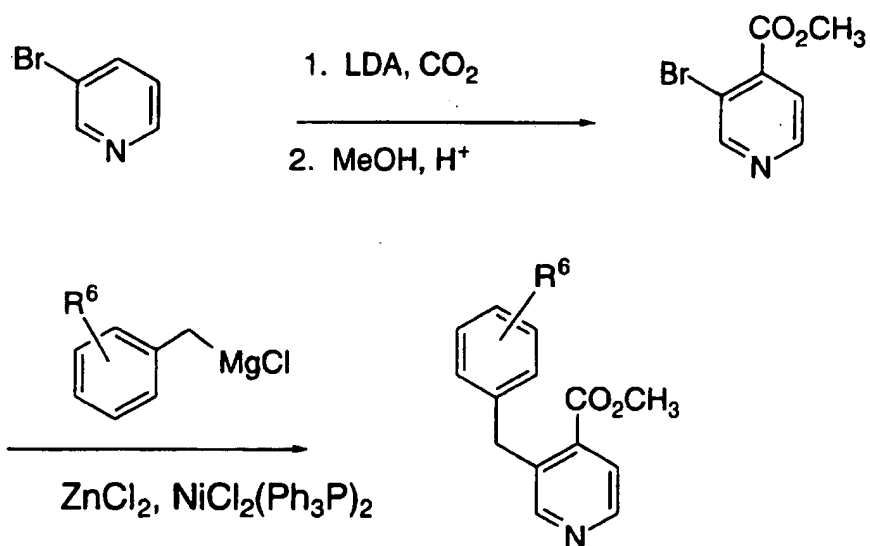
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SCHEME 2

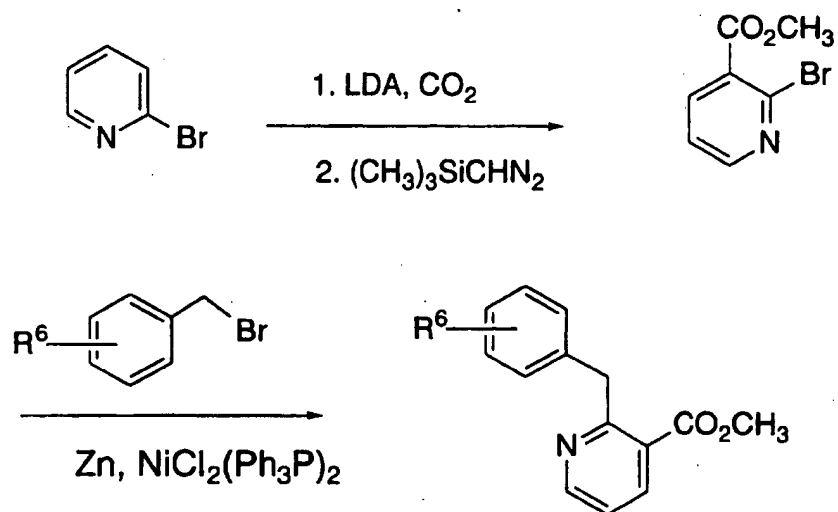
- 26 -

SCHEME 3

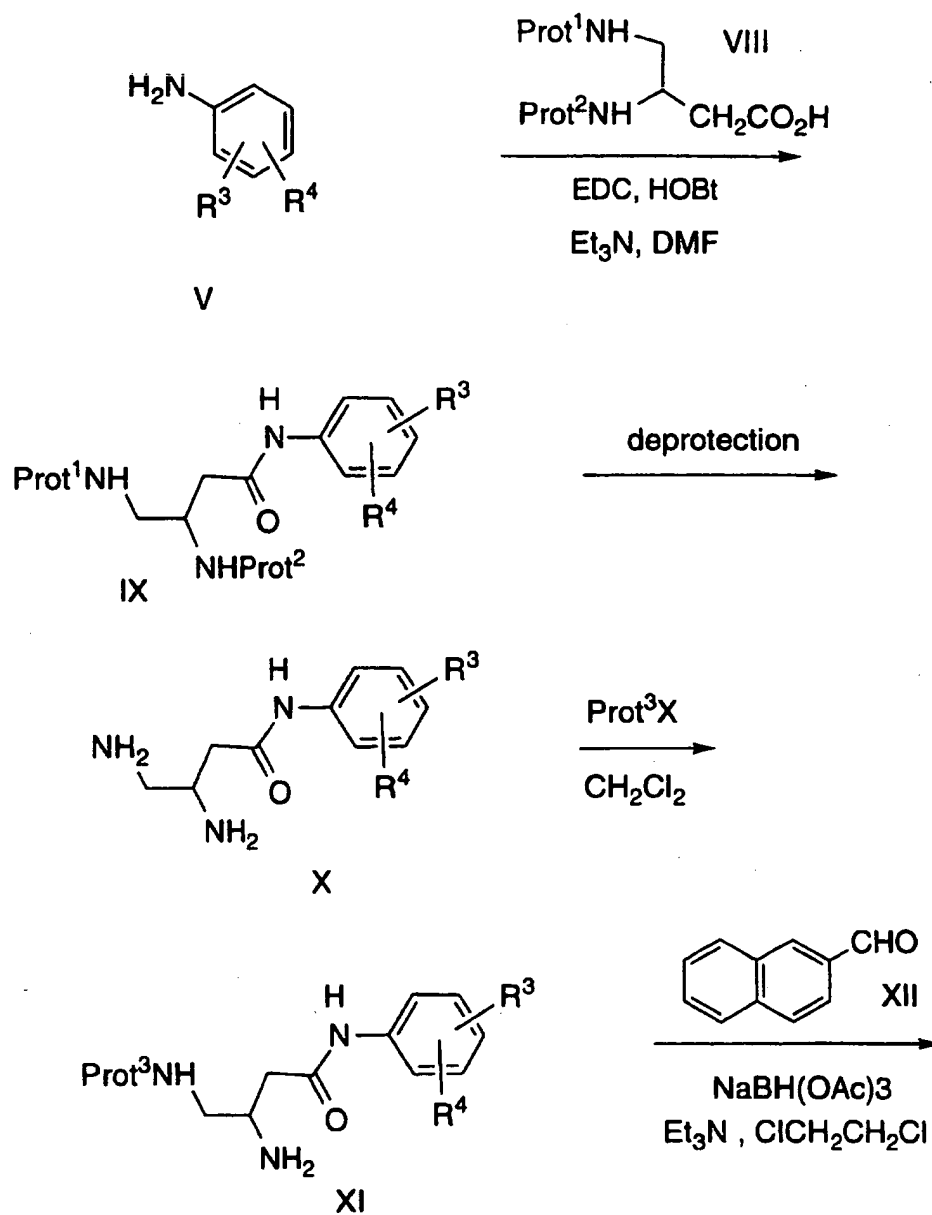
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SCHEME 4

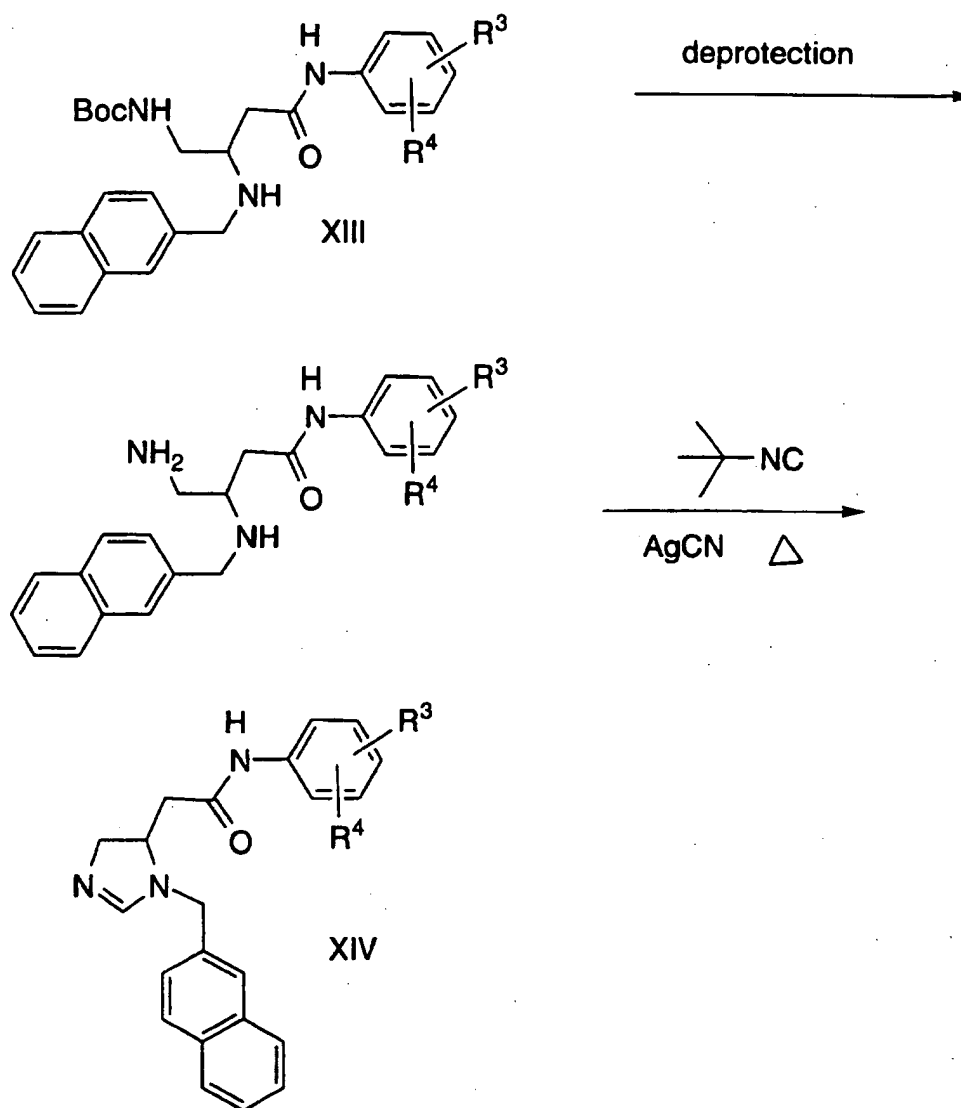
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SCHEME 5

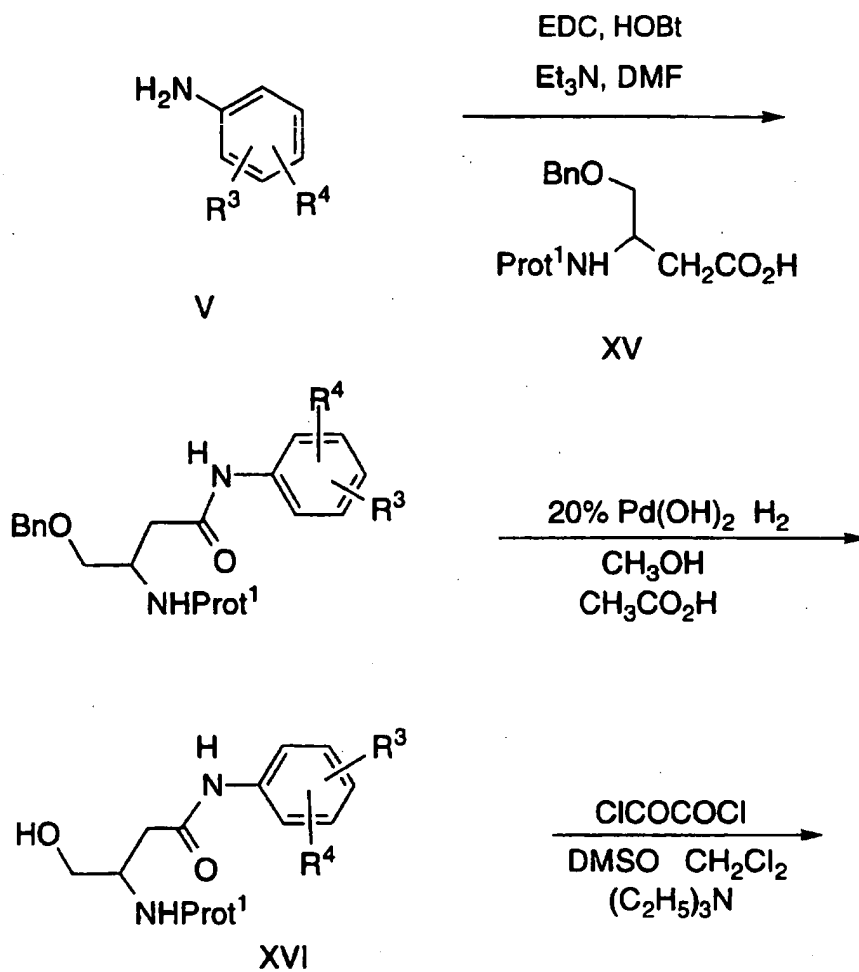
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SCHEME 6

- 29 -

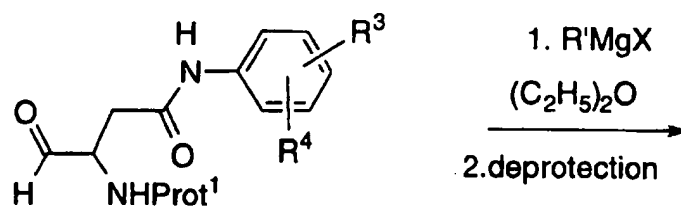
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- 30 -

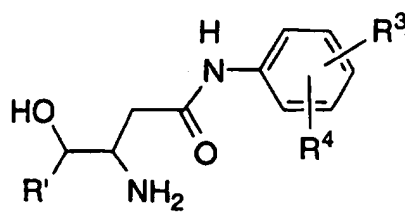
SCHEME 7



- 31 -

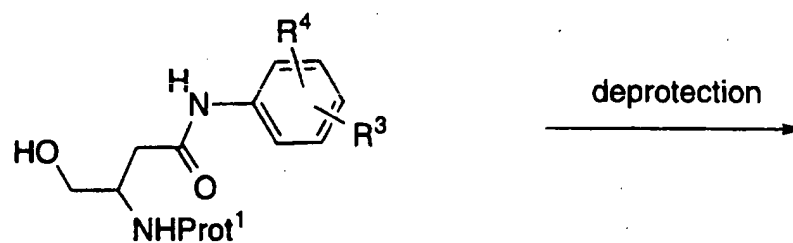
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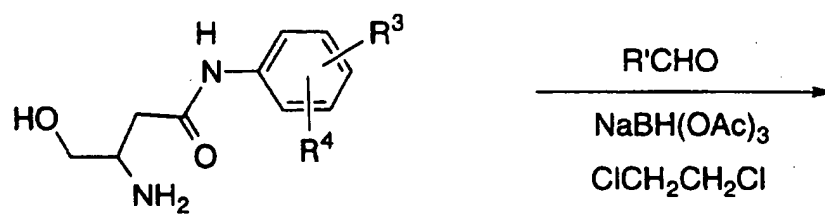


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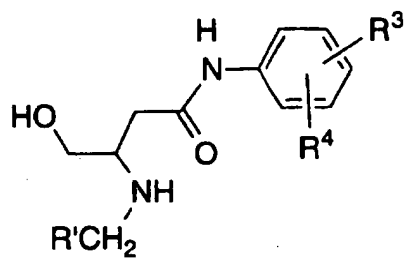
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SCHEME 8

XVI

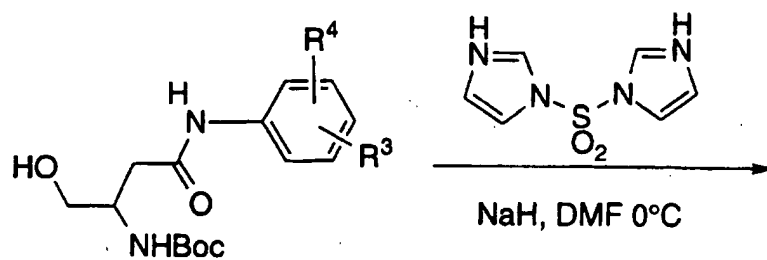


XIX

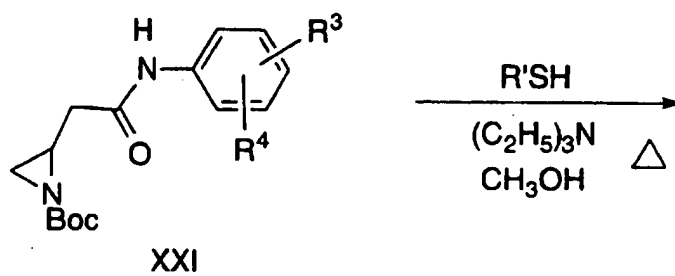


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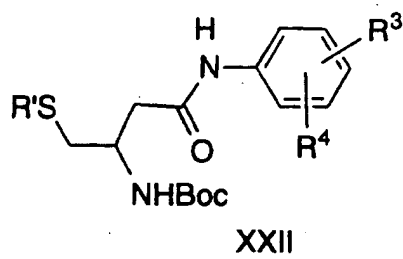
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SCHEME 9

XVIa

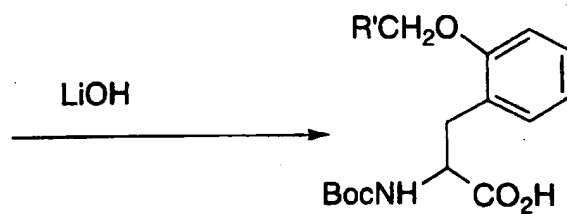
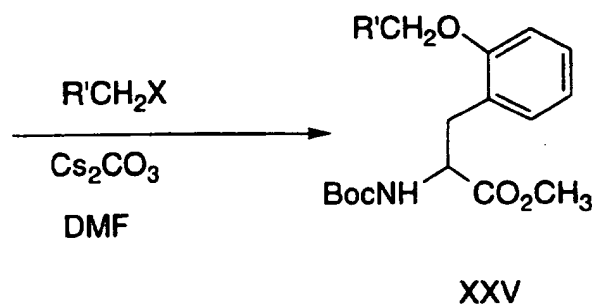
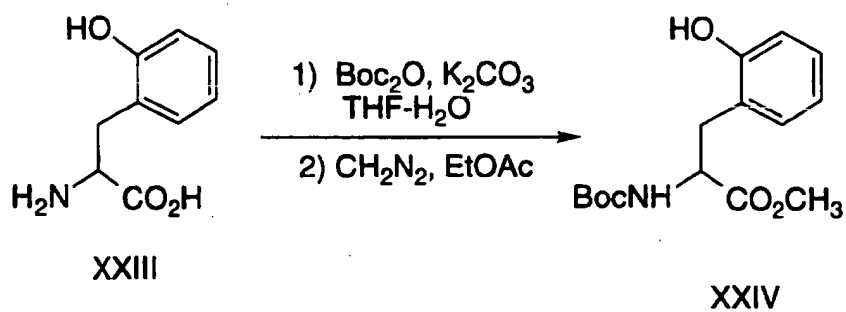


XXI

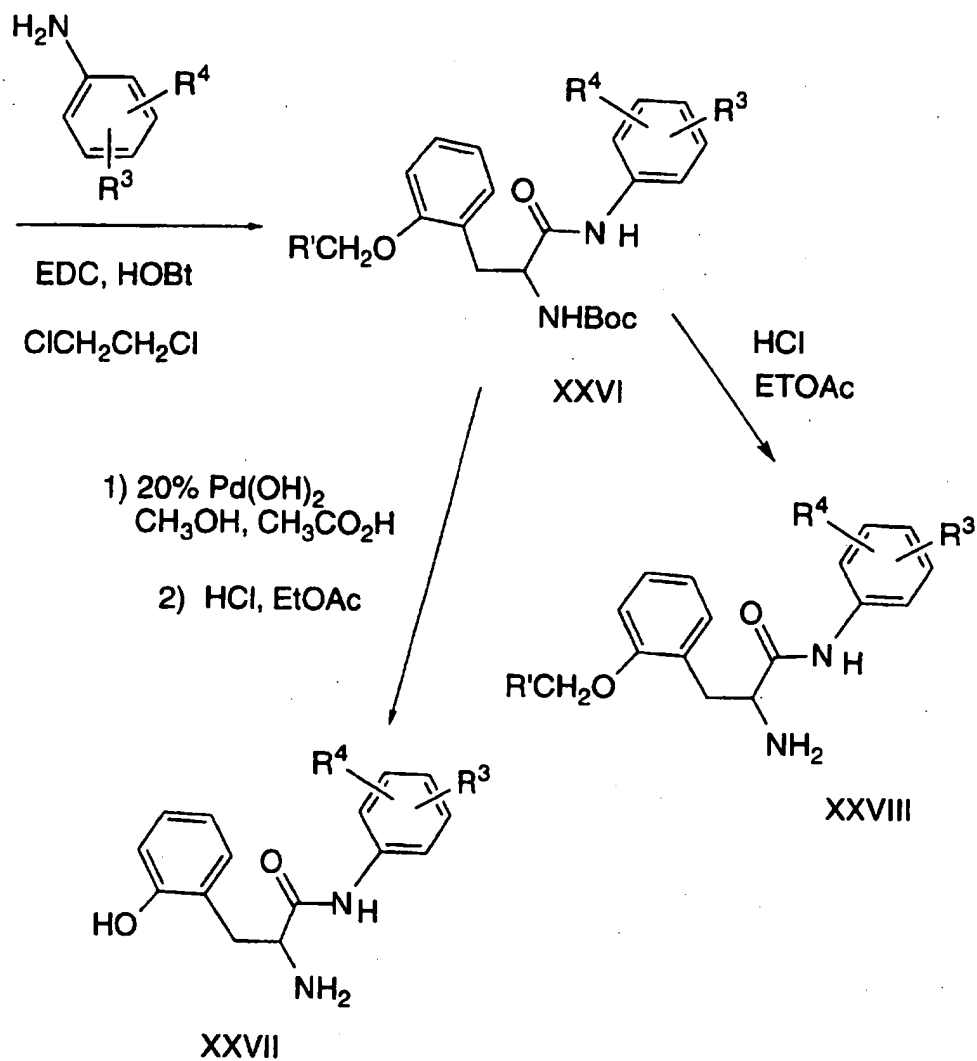


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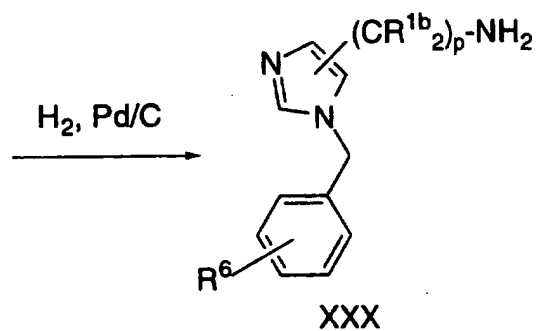
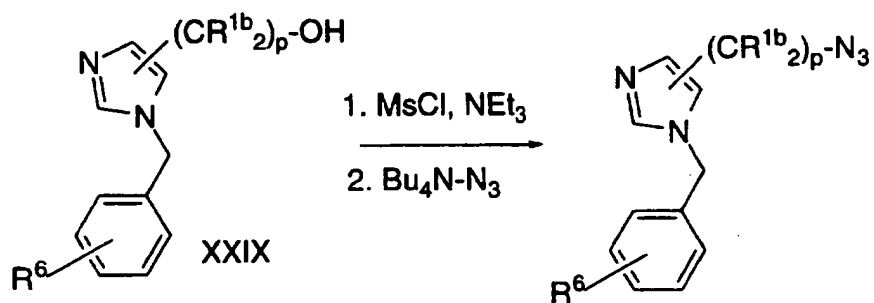
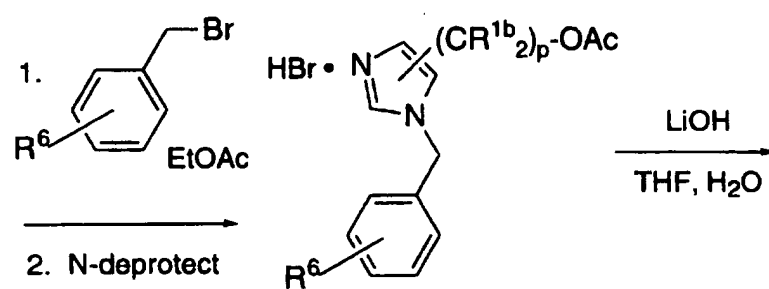
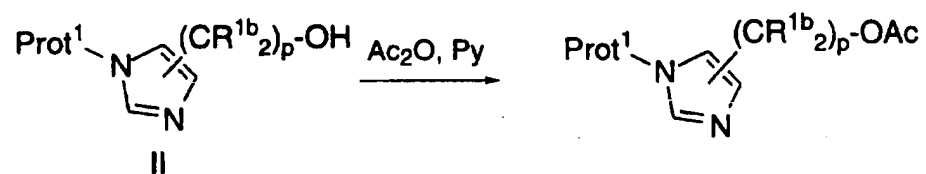
- 34 -

SCHEME 10

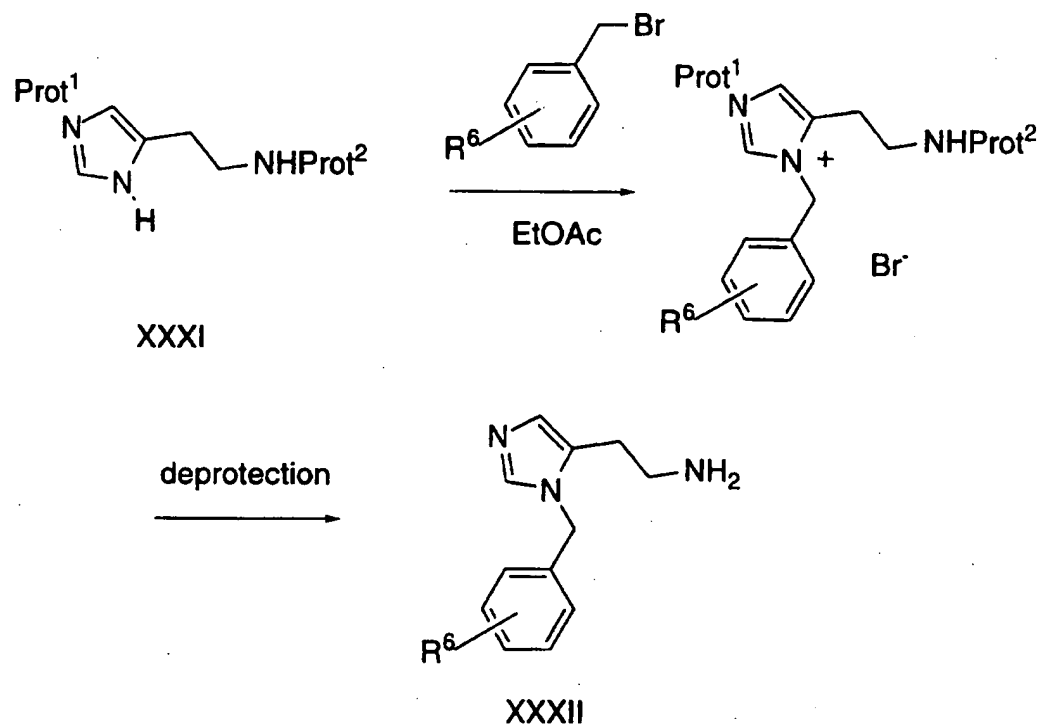
- 35 -

SCHEME 10 (continued)

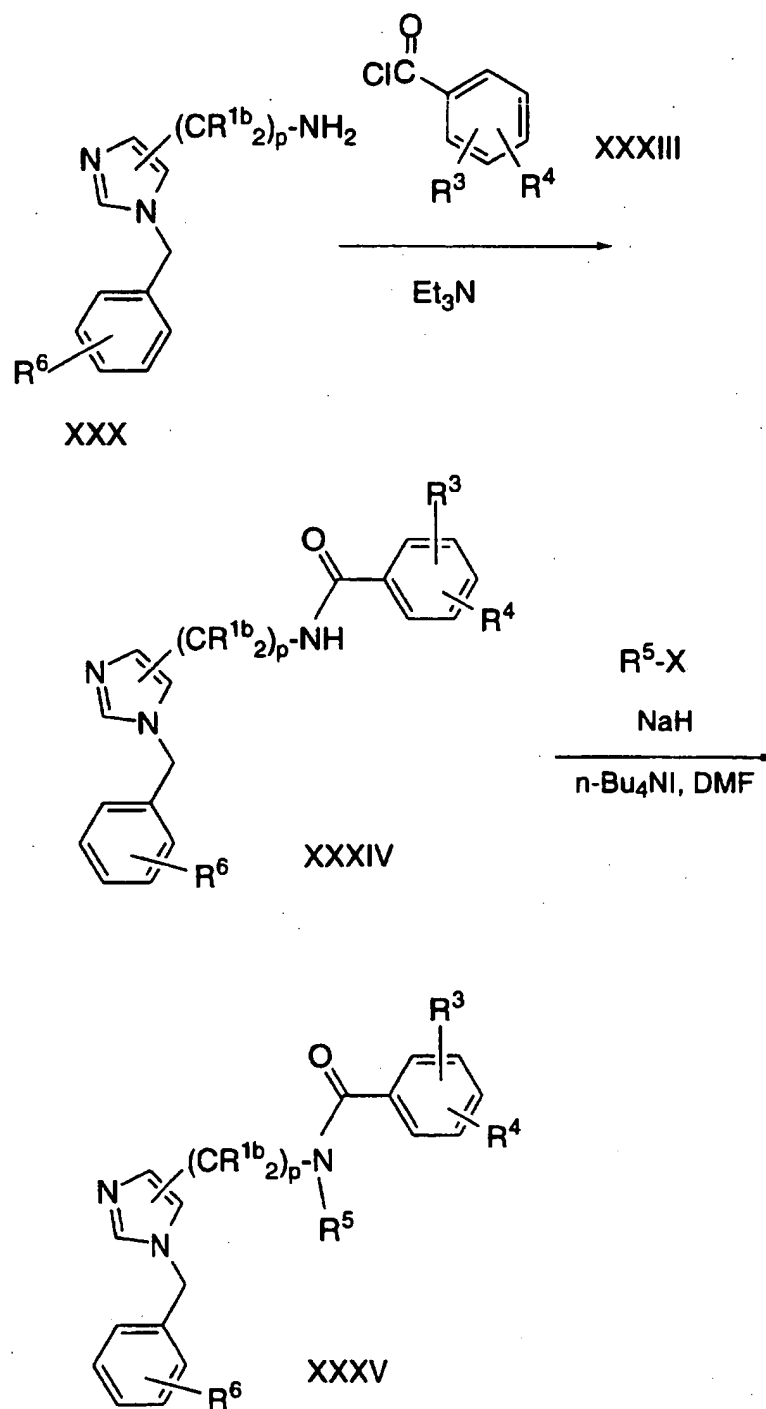
- 36 -

SCHEME 11

- 37 -

SCHEME 11 (continued)

- 38 -

SCHEME 12



- 39 -

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras formation (i.e., neurofibromin (NF-1), *neu*, *scr*, *abl*, *lck*, *fyn*) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

- 40 -

*American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in  
5 combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and  
10 topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are  
15 commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents.  
20 If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled  
25 in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers  
30 or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

- 41 -

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to

- 42 -

determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a  $K_i$  substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

### EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

#### EXAMPLE 1

N-(3-chlorophenyl)-3-[1-(4-cyanobenzyl)-5-imidazolyl]propionamide hydrochloride (1)

Step 1: Preparation of methyl 3-(4-imidazolyl)-2-propenoate (2)  
Through a suspension of urocanic acid (5.0 g) in methanol at 0 °C was bubbled HCl gas until the solution was saturated. The reaction was stirred for one hour, then concentrated *in vacuo* to dryness to provide the crude product 2 which was used in the next step without further purification.

Step 2: Preparation of methyl 3-(4-imidazolyl)propionate (3)  
To a solution of ester 2 (5.3 g) in methanol at room temperature was added 10% palladium on carbon (20 mg) under a

- 43 -

blanket of argon.. A balloon of hydrogen was applied, and the reaction was stirred for one hour. The solution was filtered, and then concentrated *in vacuo* to dryness to provide the crude product 3 which was sufficiently pure for use in the next step.

5

Step 3: Preparation of methyl 3-(1-triphenylmethyl-4-imidazolyl)-propionate (4)

To a solution of ester 3 (1.77 g) in 10 mL of dry DMF at room temperature was added triethylamine (3.25 mL). A white solid precipitated from the solution. Chlorotriphenylmethane (2.65 g) in 12 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, then poured into 40% EtOAc/hexane solution and washed with two portions of water. The organic layer was extracted with sat. aq. NaHCO<sub>3</sub> solution and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to provide the crude product 4 which was sufficiently pure for use in the next step.

Step 4: Preparation of methyl 3-[1-(4-cyanobenzyl)-5-imidazolyl]propionate (5)

A solution of 4 (4.3 g) and  $\alpha$ -bromo-*p*-tolunitrile (2.03 g) in 30 mL of EtOAc was stirred at 65 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature, concentrated *in vacuo*, and dissolved in 30 mL of methanol. The resulting solution was warmed to 60 °C for one hour, then reconcentrated *in vacuo*. The solid material was triturated to remove soluble materials, then taken up in CH<sub>2</sub>Cl<sub>2</sub>/50% aq. NaHCO<sub>3</sub> soln. The aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> and concentrated *in vacuo* to provide the crude product. Purification by silica gel chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the titled compound as a white waxy solid.

Step 5: Preparation of 3-[1-(4-cyanobenzyl)-5-imidazolyl]-propionic acid hydrochloride (6)

- 44 -

To a solution of the methyl ester 5 (1.10 g) in 10 mL of THF and 5 mL of water was added lithium hydroxide monohydrate (172 mg). After two hours, the reaction was cooled to 0 °C, and a 1 M solution of HCl/ether (8.2 mL) was added. The solution was concentrated and dried *in vacuo* next to P<sub>2</sub>O<sub>5</sub> to provide the product 6 as a white solid.

**Step 6: Preparation of *N*-(3-chlorophenyl)-3-[1-(4-cyanobenzyl)-5-imidazolyl]propionamide hydrochloride (1)**

To a 0 °C solution of acid 6 (141 mg) in 2 mL of dry DMF was added triethylamine (0.089 mL), and 3-chloroaniline (0.046 mL). 1-Hydroxybenzotriazole hydrate (80 mg) was added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (106 mg). After six hours, the reaction was poured into EtOAc, washed with sat. aq. NaHCO<sub>3</sub> solution and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to provide the crude product. Purification by silica gel chromatography (2-6% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave a white foam which was taken up in CH<sub>2</sub>Cl<sub>2</sub>, treated with 1 M HCl/ether solution, and concentrated *in vacuo*. The product hydrochloride 1 was isolated as a white powder.

FAB mass spectrum *m/e* 365 (M+1).

Analysis calculated for C<sub>20</sub>H<sub>17</sub>ClN<sub>4</sub>O • 1.00 HCl • 0.50 H<sub>2</sub>O:

C, 58.55; H, 4.67; N, 13.65;

Found: C, 58.61; H, 4.53; N, 13.47.

## EXAMPLE 2

### *In vitro* inhibition of ras farnesyl transferase

*Assays of farnesyl-protein transferase.* Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber *et al.*, *J. Biol. Chem.* 265:14701-14704 (1990), Pompliano, *et al.*, *Biochemistry* 31:3800 (1992) and Gibbs *et al.*, *PNAS* U.S.A. 86:6630-6634 (1989), respectively. Bovine

- 45 -

FPTase was assayed in a volume of 100  $\mu$ l containing 100 mM N-(2-hydroxy ethyl) piperazine-N'-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl<sub>2</sub>, 5 mM dithiothreitol (DTT), 100 mM [<sup>3</sup>H]-farnesyl diphosphate ([<sup>3</sup>H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10  $\mu$ g/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB  $\beta$ -plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [<sup>3</sup>H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer *et al.*, Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10  $\mu$ M ZnCl<sub>2</sub> and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100  $\mu$ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compound of the instant invention described in Example 1 was tested for inhibitory activity against human FPTase by the assay described above and was found to have IC<sub>50</sub> of < 10  $\mu$ M.

### EXAMPLE 3

#### 30 *In vivo* ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. *et al.*, Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75%

- 46 -

confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[<sup>35</sup>S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl<sub>2</sub>/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 mM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

#### EXAMPLE 4

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##### *In vivo* growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cells transformed by *v-Raf* and *v-Mos* maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

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Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos* are seeded at a density of  $1 \times 10^4$  cells per plate (35 mm in diameter) in



- 47 -

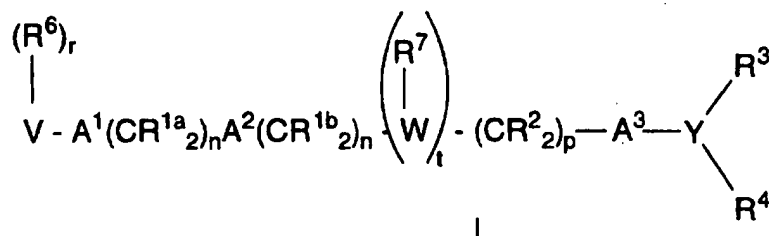
a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

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- 48 -

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula I:



5

wherein:

R<sup>1a</sup>, R<sup>1b</sup> and R<sup>2</sup> are independently selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-,
- 15 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)-NR<sup>8</sup>-;
- 20 R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, CF<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>O-, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or
- 25 unsubstituted heterocycle;

R<sup>5</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl,

- 49 -

- c) unsubstituted or substituted heterocyclic,  
 d) unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, and  
 e) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group  
 selected from unsubstituted or substituted aryl,  
 5 unsubstituted or substituted heterocyclic, unsubstituted or  
 substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-,  
 (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-,  
 (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;
- 10 R<sup>6</sup> is independently selected from:
- a) hydrogen,  
 b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-  
 C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-,  
 R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, R<sup>8</sup><sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-,  
 15 R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-, and  
 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,  
 heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub>  
 alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-,  
 R<sup>8</sup>C(O)NH-, CN, H<sub>2</sub>N-C(NH)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>,  
 20 -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>8</sup>OC(O)NH-;
- R<sup>7</sup> is selected from:
- a) hydrogen,  
 b) C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br,  
 25 R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>,  
 (R<sup>8</sup>)<sub>2</sub>N-C-(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or  
 R<sup>9</sup>OC(O)NR<sup>8</sup>-, and  
 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by perfluoroalkyl,  
 F, Cl, Br, R<sup>8</sup>O-, R<sup>9</sup>S(O)<sub>m</sub>-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, (R<sup>8</sup>)<sub>2</sub>N-  
 30 C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, N<sub>3</sub>, -N(R<sup>8</sup>)<sub>2</sub>, or  
 R<sup>9</sup>OC(O)NR<sup>8</sup>-;

R<sup>8</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and  
 aryl;

- 50 -

$R^9$  is independently selected from  $C_1$ - $C_6$  alkyl and aryl;

$A^1$  and  $A^2$  are independently selected from: a bond,  $-CH=CH-$ ,  $-C\equiv C-$ ,  
 5  $-C(O)-$ ,  $-C(O)NR^8-$ ,  $-NR^8C(O)-$ , O,  $-N(R^8)-$ ,  
 $-S(O)_2N(R^8)-$ ,  $-N(R^8)S(O)_2-$ , or  $S(O)_m$ ;

$A^3$  is selected from:  $-NR^5C(O)-$  or  $-C(O)NH-$ ;

10 V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d)  $C_1$ - $C_{20}$  alkyl wherein from 0 to 4 carbon atoms are  
 15 replaced with a heteroatom selected from O, S, and N,  
 and
- e)  $C_2$ - $C_{20}$  alkenyl,

provided that V is not hydrogen if  $A^1$  is  $S(O)_m$  and V is not hydrogen  
 if  $A^1$  is a bond, n is 0 and  $A^2$  is  $S(O)_m$ ;

20

W is a heterocycle;

Y is aryl or heteroaryl;

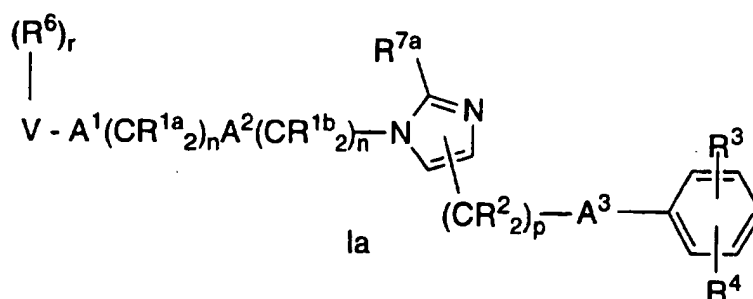
25 m is 0, 1 or 2;  
 n is 0, 1, 2, 3 or 4;  
 p is 0, 1, 2, 3 or 4;  
 r is 0 to 5, provided that r is 0 when V is hydrogen; and  
 t is 0 or 1;

30

or an optical isomer or pharmaceutically acceptable salt thereof.

2. A compound which inhibits farnesyl-protein  
 transferase of the formula Ia:

- 51 -



wherein:

- 5    R<sup>1a</sup> and R<sup>1b</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;
- R<sup>2</sup> is independently selected from:
- 10        a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;
- 15    R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted
- 20        heterocycle;
- R<sup>5</sup> is selected from:
- a) hydrogen,
- and
- 25        b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-,

- 52 -

$(R^9)S(O)_m-$ ,  $(R^8)C(O)NH-$ ,  $H_2N-C(NH)-$ ,  $(R^8)C(O)-$ ,  
 $(R^8)OC(O)-$ ,  $N_3$ ,  $CN$   $(R^9)OC(O)NR^8-$ ;

$R^6$  is independently selected from:

- 5           a) hydrogen,  
             b)  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_1-C_6$   
                 perfluoroalkyl, F, Cl,  $R^8O-$ ,  $R^8C(O)NR^8-$ , CN,  $NO_2$ ,  
                  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  $-N(R^8)_2$ , or  
                  $R^9OC(O)NR^8-$ , and  
 10           c)  $C_1-C_6$  alkyl substituted by  $C_1-C_6$  perfluoroalkyl,  $R^8O-$ ,  
                  $R^8C(O)NR^8-$ ,  $(R^8)_2N-C(NR^8)-$ ,  $R^8C(O)-$ ,  $R^8OC(O)-$ ,  
                  $-N(R^8)_2$ , or  $R^9OC(O)NR^8-$ ;

$R^{7a}$  is hydrogen or methyl;

- 15            $R^8$  is independently selected from hydrogen,  $C_1-C_6$  alkyl, benzyl and  
                 aryl;

$R^9$  is independently selected from  $C_1-C_6$  alkyl and aryl;

- 20            $A^1$  and  $A^2$  are independently selected from: a bond,  $-CH=CH-$ ,  $-C\equiv C-$ ,  
                  $-C(O)-$ ,  $-C(O)NR^8-$ , O,  $-N(R^8)-$ , or  $S(O)_m$ ;

$A^3$  is selected from:  $-NR^5C(O)-$  or  $-C(O)NH-$ ;

- 25           V is selected from:

- a) hydrogen,  
             b) heterocycle selected from pyrrolidinyl, imidazolyl,  
                 pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl,  
                 quinolinyl, isoquinolinyl, and thienyl,  
 30           c) aryl,  
             d)  $C_1-C_{20}$  alkyl wherein from 0 to 4 carbon atoms are  
                 replaced with a heteroatom selected from O, S, and N,  
                 and

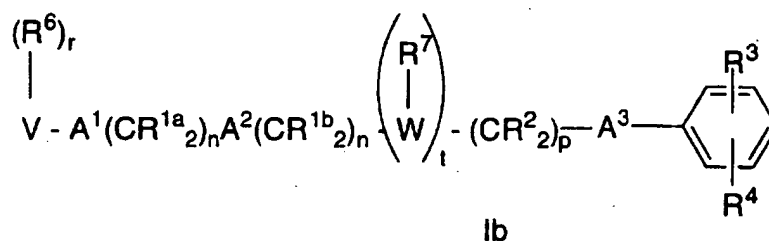
- 53 -

e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and  
provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen  
if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

- 5    m is            0, 1 or 2;  
     n is            0, 1, 2, 3 or 4;  
     p is            0, 1, 2, 3 or 4; and  
     r is            0 to 5, provided that r is 0 when V is hydrogen;

10   or an optical isomer or pharmaceutically acceptable salt thereof.

3.    A compound which inhibits farnesyl-protein  
transferase of the formula Ib:



15

wherein:

R<sup>1a</sup> and R<sup>1b</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub>  
alkyl;

20

R<sup>2</sup> is independently selected from:

- a)    hydrogen,  
b)    aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub>  
      alkenyl,  
25    c)    C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,  
      heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;

R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>,  
NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-

- 54 -

C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN,  
(R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or  
unsubstituted aryl and substituted or unsubstituted  
heterocycle;

5

R<sup>5</sup> is selected from:

a) hydrogen,

and

b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group  
selected from unsubstituted or substituted aryl,  
unsubstituted or substituted heterocyclic, unsubstituted or  
substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-,  
(R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-,  
(R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

15

R<sup>6</sup> is independently selected from:

a) hydrogen,

b) C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub>  
perfluoroalkyl, F, Cl, R<sup>8</sup>O-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>,  
(R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, -N(R<sup>8</sup>)<sub>2</sub>, or  
R<sup>9</sup>OC(O)NR<sup>8</sup>-, and  
c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>8</sup>O-,  
R<sup>8</sup>C(O)NR<sup>8</sup>-, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-,  
-N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-;

25

R<sup>7</sup> is selected from: hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>8</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and  
aryl;

30

R<sup>9</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-,  
-C(O)-, -C(O)NR<sup>8</sup>-, O, -N(R<sup>8</sup>)-, or S(O)<sub>m</sub>;



- 55 -

A<sup>3</sup> is selected from: -NR<sup>5</sup>C(O)- or -C(O)NH-;

V is selected from:

- 5           a) hydrogen,  
             b) heterocycle selected from pyrrolidinyl, imidazolyl,  
                     pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl,  
                     quinolinyl, isoquinolinyl, and thienyl,  
             c) aryl,  
 10           d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are  
                     replaced with a heteroatom selected from O, S, and N,  
                     and  
             e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and  
 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen  
 15 if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

W is a heterocycle selected from pyrrolidinyl, pyridinyl, thiazolyl,  
 pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

- 20   m is           0, 1 or 2;  
      n is           0, 1, 2, 3 or 4;  
      p is           0, 1, 2, 3 or 4;  
      r is           0 to 5, provided that r is 0 when V is hydrogen; and  
      t is           1;

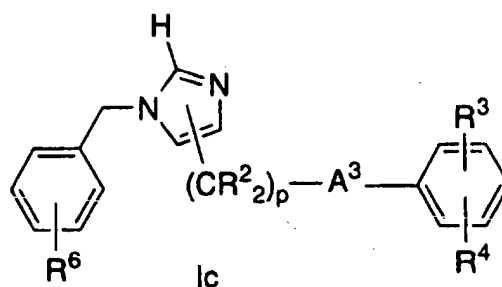
25

or an optical isomer or pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the formula

Ic:

- 56 -



wherein:

R<sup>1b</sup> is independently selected from:

- 5       a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;

10

R<sup>2</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

15

20   R<sup>5</sup> is selected from:

- a) hydrogen,
- and
- b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

25

- 57 -

$R^6$  is independently selected from:

- a) hydrogen,
- b) C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>8</sup>O-, R<sup>8</sup>C(O)NR<sup>8</sup>-, CN, NO<sub>2</sub>, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>8</sup>O-, R<sup>8</sup>C(O)NR<sup>8</sup>-, (R<sup>8</sup>)<sub>2</sub>N-C(NR<sup>8</sup>)-, R<sup>8</sup>C(O)-, R<sup>8</sup>OC(O)-, -N(R<sup>8</sup>)<sub>2</sub>, or R<sup>9</sup>OC(O)NR<sup>8</sup>-;

$R^8$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and aryl;

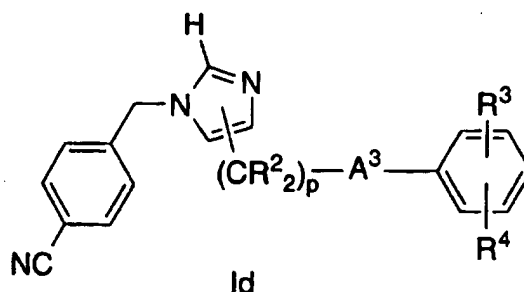
$R^9$  is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

$A^3$  is selected from: -NR<sup>5</sup>C(O)- or -C(O)NH-;

m is 0, 1 or 2; and  
p is 0, 1, 2, 3 or 4;

or an optical isomer or pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1 of the formula  
Id:



wherein:

- 58 -

R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, R<sup>8</sup>O-, -N(R<sup>8</sup>)<sub>2</sub> or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R<sup>8</sup>O-, or -N(R<sup>8</sup>)<sub>2</sub>;

R<sup>2</sup> are independently selected from: hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>3</sup> and R<sup>4</sup> are independently selected from F, Cl, Br, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN, (R<sup>9</sup>)OC(O)NR<sup>8</sup>-, C<sub>1</sub>-C<sub>20</sub> alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R<sup>5</sup> is selected from:

- a) hydrogen,
- and
- b) C<sub>1</sub>-C<sub>6</sub> alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, N(R<sup>8</sup>)<sub>2</sub>, CF<sub>3</sub>, NO<sub>2</sub>, (R<sup>8</sup>)O-, (R<sup>9</sup>)S(O)<sub>m</sub>-, (R<sup>8</sup>)C(O)NH-, H<sub>2</sub>N-C(NH)-, (R<sup>8</sup>)C(O)-, (R<sup>8</sup>)OC(O)-, N<sub>3</sub>, CN (R<sup>9</sup>)OC(O)NR<sup>8</sup>-;

R<sup>8</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl and aryl;

R<sup>9</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

A<sup>3</sup> is selected from: -NR<sup>5</sup>C(O)- or -C(O)NH-;

- 59 -

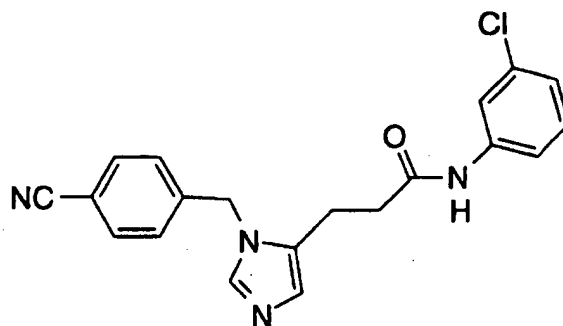
m is 0, 1 or 2; and  
p is 0, 1, 2, 3 or 4;

or an optical isomer or pharmaceutically acceptable salt thereof.

5

6. A compound which inhibits farnesyl-protein transferase which is:

*N*-(3-chlorophenyl)-3-[1-(4-cyanobenzyl)-5-imidazolyl]propionamide  
10 hydrochloride (1)



or a pharmaceutically acceptable salt thereof.

15

7. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

20

8. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

25

9. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

- 60 -

10. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 6.

5 11. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

10 12. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

15 13. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

20 14. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

15. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

25 16. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

30 17. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

- 61 -

18. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

5           19. A method for treating neurofibromen benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

10           20. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

15           21. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

20           22. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

25           23. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/01354

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/415; C07D 233/66, 233/90, 233/60, 233/54; 233/61.

US CL : 514/399, 400; 548/336.1, 338.1.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/336.1, 338.1; 514/399, 400.1.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CHEMICAL ABSTRACTS

INDEX CHIMICUS

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,534,537 A (CICCARONE ET AL.) 09 July 1996, see entire document.	1-23
A, P	US 5,571,792 A (BOLTON ET AL.) 05 November 1996, see entire document.	1-23
A, P	US 5,578,629 A (CICCARONE ET AL.) 26 November 1996, see entire document.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

02 MAY 1997

Date of mailing of the international search report

02 JUN 1997

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